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t(15;21)(q15;q22.1)pat Resulting in Partial Trisomy and Partial Monosomy of Chromosomes 15 and 21 in Two Offspring

Dvorah Abeliovich, Judith Dagan, Israela Lerer, Shira Silberstein, Mariassa Bat-Miriam Katznelson, and Moshe Frydman

Department of Human Genetics, Hadassah University Hospital, Hebrew University Hadassah Medical School, Jerusalem (D.A., J.D., I.L., S.S.); Genetic Institute, Sheba Medical Center, Tel Hashomer (M.B-M.K.); and Department of Pediatrics, Hasharon Hospital, Petah Tiqva Tel-Aviv University Sackler Medical School, Tel-Aviv (M.F.), Israel

Two sibs, carriers of unbalanced products of the translocation t(15;21)(q15;q22.1)pat, are described. The sister had Prader-Willi syndrome due to deletion 15 (pter > q15) and partial trisomy 21 (pter > q22.1); her brother had partial trisomy 15 (pter > q15) and partial monosomy 21 (pter > q22.1). The translocation breakpoint on chromosome 21 was located proximal to the SOD1 gene, within a region of 4.0 cM (2.3 Mb) between the loci D21S217 and D21S213. The correlations between the clinical presentation and the molecular findings of the two sibs are discussed in relation to other patients with partial trisomy and monosomy 21. © 1996 Wiley-Liss, Inc.

KEY WORDS: Prader-Willi syndrome, partial trisomy 21, partial monosomy 21, duplication 15(pter > q15), translocation breakpoint, D21S217, D21S213

INTRODUCTION

The clinical delineation of syndromes that are associated with full or partial monosomies and trisomies is an important tool in the assignment of genes and clinical signs to a particular chromosomal segment. The physical map of chromosome 21 provides an accurate means for the definition of the duplicated or the deleted segments in partial trisomies and monosomies 21 and the phenotype-genotype correlation allows the construction of a phenotypic map. Such correlations have been presented for partial trisomies of chromosome 21 [Epstein et al., 1991; Korenberg et al., 1994] and for partial monosomies 21 [Chettouh et al., 1995].

We had the opportunity to analyze two sibs, unbalanced products of a paternal translocation t(15;21)(q15;q22.1) resulting in partial trisomy 21 and partial monosomy 15 in the sister and partial monosomy 21 and partial trisomy 15 in her brother. We defined the translocation breakpoint on chromosome 21 and carefully examined the patients. A genotype-phenotype correlation in each of the patients is discussed in respect to other cases with partial trisomy or monosomy of chromosome 21.

The Patients

Patient II-1. A 13-year-old girl was referred because of mental retardation and obesity. She had a mentally retarded brother; her parents were healthy and non-consanguineous. The patient, II-1, was born at 36 weeks of gestation by forceps delivery. During pregnancy the fetal movements were markedly reduced. Her birth weight was 2,100 g (10th centile) and Apgar score was 8/10, OFC was 32 cm (25th centile). At birth, general hypotonia and congenital dislocation of the hips were noted. Early feeding problems, poor head control and hypotonia persisted during the first year of life. She sat alone at 18 months and walked at 3 years. Voracious appetite began around age 1 y and morbid obesity developed gradually. She weighed 17 kg at age 2 y, 28 kg at 4 y, 51 kg at 7 y and 101 kg at 13 y. She had bilio-pancreatic deviation at age 13 y, however, following the operation she did not have any change in her feeding habits. Beginning at age 1 y she had several convulsive episodes, however, the electroencephalogram (EEG) and brain computed tomography (CT) were normal. At age 11 y she had pneumoccocal pneumonia complicated by sepsis, transitory diabetic ketoacidosis and Coombs-positive thrombocytopenia (Evans syndrome). At age 13 y her OFC was 52 cm (10th centile), her height was 145 cm (3rd centile) and she was prepubertal at Tanner 2. She was moderately mentally retarded and her speech was slurred and had a nasal

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Address reprint requests to Dvorah Abeliovich, Ph.D., Department of Human Genetics, Hadassah Hebrew University Hospital, Ein Kerem, Jerusalem 91120, Israel.

quality. Her face (Fig. 1a) was flat and rounded, the nasal bridge normal and the nose bulbous. The anterior hairline was low and the palpebral fissures were upslanted without epicanthus, she had moderate synophris and long and thick eyelashes, severe myopia and keratoconus. The philtrum was short and flat, the lips thin and the upper lip was barely visible. Class 3 malocclusion with prognathism was present and the corners of the mouth were down-turning. The neck was apparently short without the typical flatness seen in Down syndrome. The heart was normal. Cubitus valgus (20°) and limited elbow extension (15°) were present. The hands were broad and the fingers tapering; the 4th metacarpal was somewhat short without clinodactyly, the feet were flat. Below the left breast, a segmental hypopigmented area with irregular borders appeared at age 11 y. Muscle tone was decreased, coordination was poor but no pyramidal or extrapyramidal signs were found.

Patient II-2. Brother of patient II-1 was born after 38 weeks of an uncomplicated pregnancy. Birth weight was 2,400 g (3rd centile) with Apgar scores 9/10. His cry was weak and high-pitched. Increased muscle tone and extreme jitteriness were noted after birth and persisted for several months. Stiff hips, clasped thumbs, clenched fingers, flexed toes and left calcaneovalgus were treated with physiotherapy and casting. He had scrotal hypoplasia and bilateral cryptorchidism and had surgical intervention at age 2 y, an atrophic left testicle was found. His motor development was normal, but speech was late to develop. During infancy, withdrawn behavior and extreme anxiety were the predominant complaints. At age 7 y he had mild to moderate mental retardation and attended a special education program. His behavior was aggressive with temper tantrums, he was withdrawn and had a short attention span. His height was 115 cm (10th centile), weight 21.5 kg (25th centile) and OFC 50 cm (10th centile). He had an odd posture because of flexible dorsal kyphosis and bent knees (Fig. 1b). The face was triangular with pointed chin, the anterior hairline was low, the eyes were deep-set and the palpebral fissures slightly downslanting, the irises were dark brown with convergent strabismus. The ears were large and protruding with normal shape and position, the neck was somewhat short. The fingers were tapering and the left thumb could not be fully extended. He had a wide gap between the 1st and 2nd toes and the lateral toes were curved and widely spaced. Muscle tone was normal, coordination was decreased and he had brisk reflexes.

Dermatoglyphic findings. Each of the patients had a unique dermatoglyphic deviation (the details are given in Table I). The most outstanding findings were the following:

In patient IL-1, very high total ridge count (>212) that could be attributed to the 9 very large whorls and a single loop. The main line index was low because the termination point of the radiant A was at position I. The a-b ridge count in this patient was very high due to

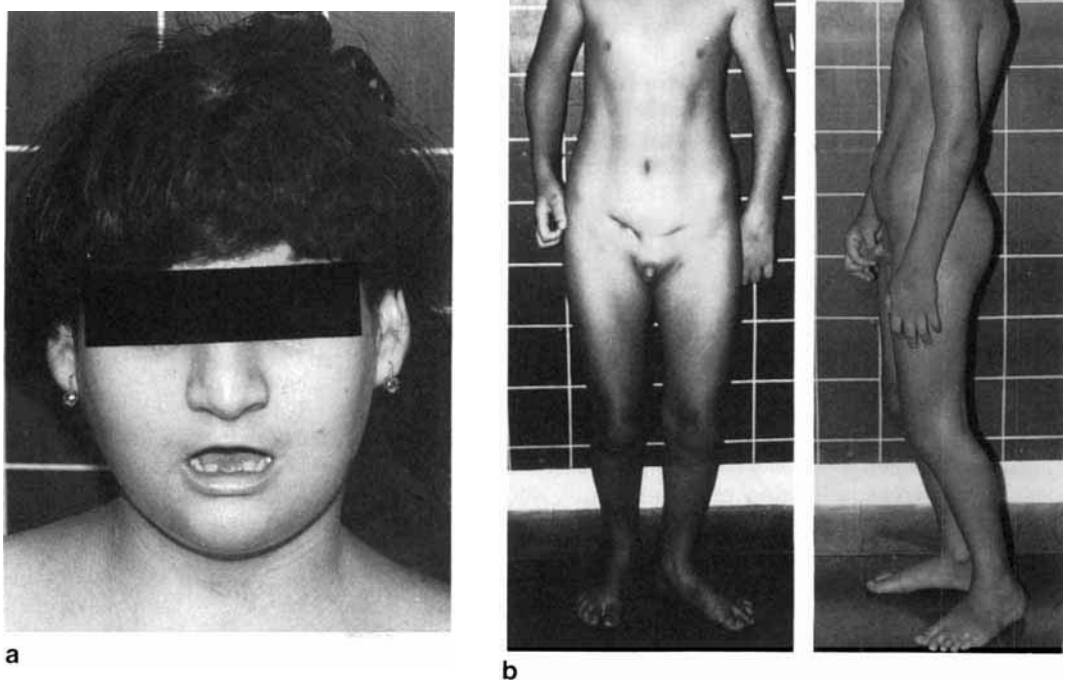


Fig. 1. **a**: Patient II-1, age 13.5 y. Lack of similarity to facial appearance of Down syndrome can be appreciated. **b**: Patient II-2, age 7 y. Note the peculiar posture, eunuchoid body build, abnormal genitalia and lack of striking facial abnormality.

TABLE I. Dermatoglyphic Findings*

	Patient II-1		Patient II-2	
Digital pattern	Left	Right	Left	Right
I	W	W	A	A
II	W	W	UL	UL
III	W	W	UL	UL
IV	W	W	UL	W
V	UL	W	UL	UL
Total ridge count	>212		100	
IIIrd interdigital pattern	C^{abort}		C^{abort}	
a-b ridge count	104		85	
Maximal atd angle	92°		87°	
Main line index	3.5		7.9	
Termination of A	1	1	1	3
Termination of D	2	4	6	6
Toe pattern				
I	L^f	L^t	A^{tented}	L^f
Hallucal pattern	L^d	L^d	A^{tented}	L^d

*W = whorle; A = arch; UL = ulnar loop; f = fibular; t = tibial; d = distal.

radial displacement of triradius 'a' below the index. In patient II-2, the shape of some of the digital ulnar loops were high and L-shaped; this pattern is typical to Down syndrome [Penrose and Smith, 1966]. The presence of arches on both thumbs is seen with various chromosomal aberrations.

MATERIALS AND METHODS

Cytogenetic Analysis

Peripheral blood lymphocytes were cultured according to standard techniques [Gosden et al., 1992]. For high resolution analysis banding, methotrexate (MTX) was applied to the cultures. G-banding was performed according to the standard techniques [Benn and Perle, 1992].

DNA Analysis

Genomic DNA was extracted according to standard techniques. Short tandem repeat sequence polymorphisms were analyzed as previously described [Lerer et al., 1994]. The polymerase chain reaction (PCR) products were separated on 8% denatured (6 M urea) polyacrylamide gel, 400 V overnight. The detection of the amplified fragments was by silver staining. In silver staining, each allele is represented by two bands with their shadow bands and not by one band which is seen in the conventional isotopic labelling. The sequences of oligonucleotide primers were retrieved from the Genome Data Base (GDB) and as previously described [Lerer et al., 1994]. Parent-of-origin specific DNA methylation sites at the locus D15S63 were analyzed by Southern hybridization, using the DNA probe PW71 and genomic digestion by either Hind III + Hpa II [Dittrich et al., 1992] or Bgl II + Cfo I [Dittrich et al., 1993]. The relative intensity of the autoradiographic bands was scanned by phospho-image analyzer.

RESULTS

Cytogenetic Results

G-banding analysis of the two patients and their parents showed a balanced translocation t(15;21)(q15;q22) in the father (Fig. 2a) and two different unbalanced

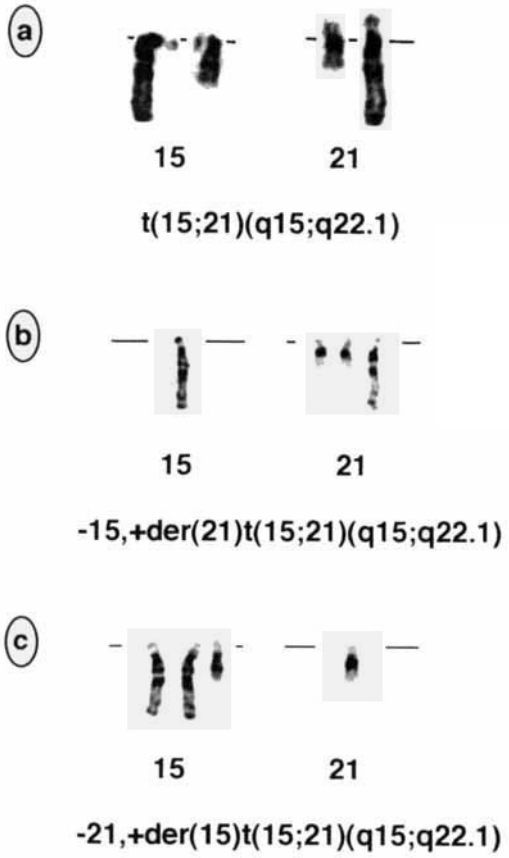


Fig. 2. **a**: Partial karyotype of the father, (**b**) the daughter, patient II-1, and (**c**) the son, patient II-2.

karyotypes in the children. The karyotype of patient IL-1 was 46,XX,−15,+der(21)t(15;21)(q15;q22.1) (Fig. 2b) and that of patient IL-2, 46,XY,−21,+der(15)t(15;21)(q15;q22.1) (Fig. 2c). As a result, patient IL-1 had a deletion of 15 (pter > q15) of paternal origin and partial trisomy 21 (pter > q22.1); her brother IL-2 had partial trisomy 15 (pter > q15) and partial monosomy 21 (pter > q22.1). Following the cytogenetic diagnosis of the translocation, prenatal diagnosis was performed in two consecutive pregnancies; the first resulted in a normal 46,XX karyotype, the second fetus had an abnormal karyotype similar to that of patient II-2, 46,XX, −21,+der(15)t(15;21)(q15;q22.1). This pregnancy was terminated at 21 weeks of gestation. The fetus was an eumorphic female; her length was 24 cm (~50th centile), crown-rump length 16.5 cm (~50th centile), and OFC 18.2 cm (~50th centile). Autopsy was not permitted.

Determination of the Translocation Breakpoint on Chromosome 21

The segregation of polymorphic markers of chromosome 21 allowed us to localize the breakpoint between two markers of known map position (Fig. 3). Each marker that appeared in a single dose in patient II-2 and in a triple dose in patient II-1 is proximal to the breakpoint. Markers that reside distal to the breakpoint appeared in two doses in both offspring (Fig. 4). A summary of the segregation analysis is given in Figure 5;

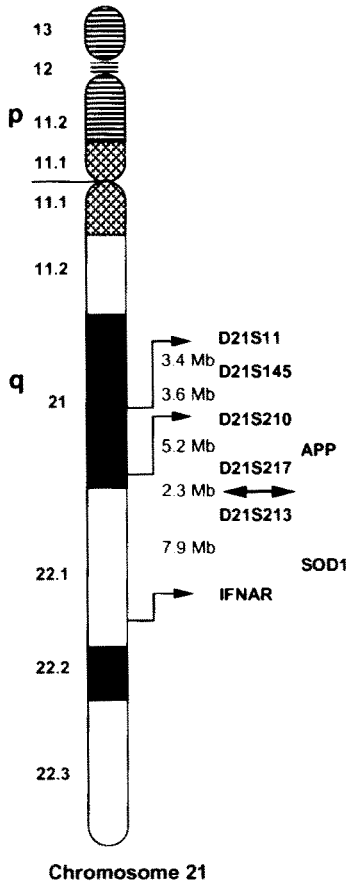


Fig. 3. Schematic presentation of chromosome 21 and the DNA polymorphic markers around the translocation breakpoint (the physical distances according to Lawrence et al. [1993]).

the closest markers to the breakpoint were D21S217 on the proximal side and D21S213 on the distal side. The distance between them is about 4 cM or 2.3 Mb [Lawrence et al., 1993; McInnis et al., 1993].

Analysis of PWS/AS Region on Chromosome 15

The analysis of the Prader-Willi/Angelman syndrome (PWS/AS) region included segregation analysis of polymorphic markers and the analysis of parent-of-origin specific DNA methylation sites at the D15S63 locus using the DNA probe PW71. Patient II-1 had no paternal contribution for the loci D15S128, GABRB3 and D15S97. At D15S63, only the methylated site was present, indicating the absence of paternal contribution at this region. Double paternal contribution to patient IL-2, was evident at the loci D15S11 and D15S128 (Fig. 5) with a double dose of the nonmethylated site at the parent-of-origin specific DNA methylation site at D15S63 locus (not shown).

DISCUSSION

Partial monosomy and trisomy of chromosomes 21 result in partial syndromes of full trisomy and monosomy, depending on the size and the genetic content of the unbalanced segments. In an attempt to assign individual clinical signs of Down syndrome (DS) and of monosomy 21, the phenotypic expression in patients with partial trisomy or monosomy of chromosome 21 is correlated to the exact breakpoint in that chromosome. This approach provided a means to map putative genes responsible for particular traits in Down syndrome [Epstein et al., 1991; Korenberg et al., 1994] and monosomy 21 [Chettouh et al., 1995].

The familial translocation that we present t(15;21)(q15;q22.1)pat resulted in two sibs with unbalanced karyotypes: the girl (II-1) had partial monosomy 15 (pter > q15) and partial trisomy 21 (pter > q22.1), the

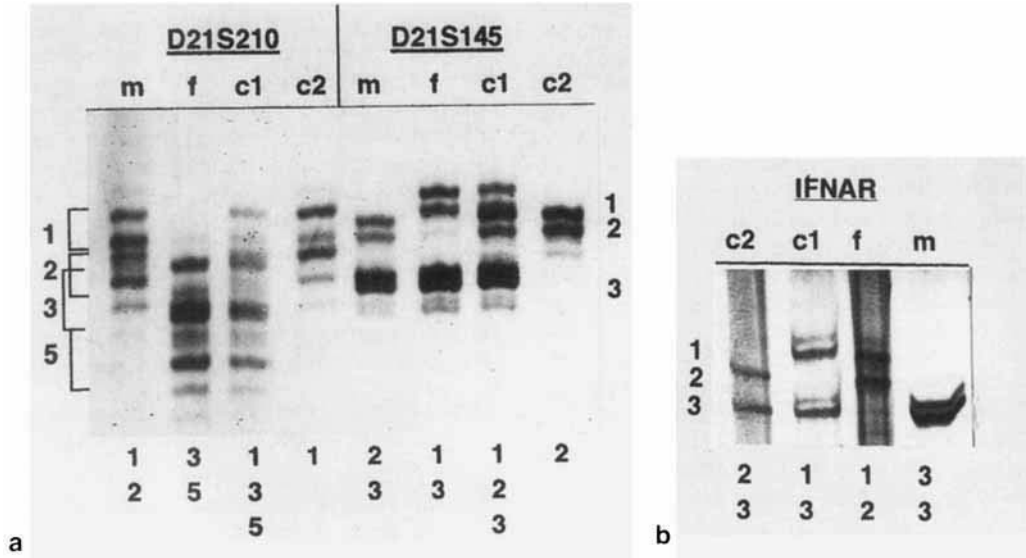
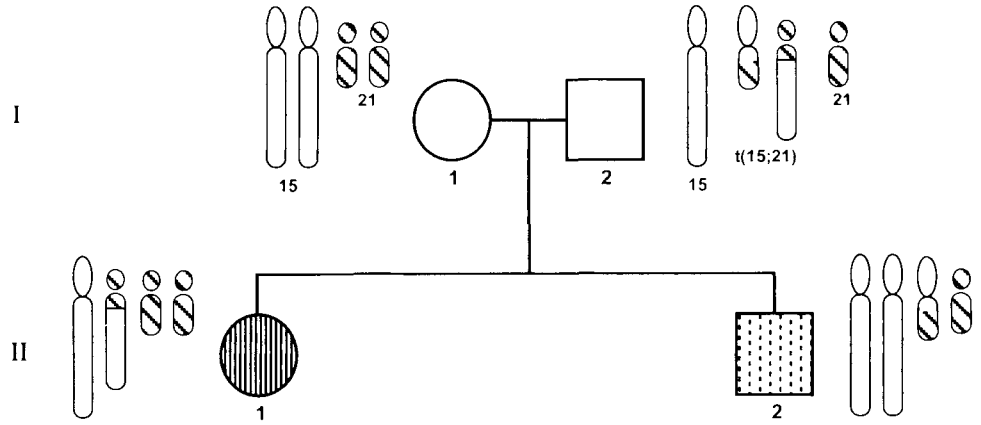


Fig. 4. Patterns of (CA)n repeats polymorphisms of the parents and the patients. m, mother, f, father, c1, patient II-1, c2, patient II-2. The interpretation of the genotype is given underneath each lane. **a**: Loci D21S145 and D21S210. **b**: Locus IFNAR. Note the three alleles of D21S145 and D21S210 in patient II-1 and a single allele in patient II-2, in IFNAR locus both patients had each one paternal allele and one maternal alleles.



chromosome 21	Patient II-1	Mother	Father	Patient II-2
D21S11	4-3-4	4-1	3-4	4
D21S145	2-1-3	2-3	1-3	2-*
D21S210	1-3-5	1-2	3-5	1-*
D21S217	2-1-4	2-1	1-4	2-*
D21S213	2-2	2-2	2-1	2-1
IFNAR	3-1	3-3	1-2	3-2
chromosome 15				
D15S11	8	5-8	6-8	5-6-8
D15S63	6/*	6-4.4	6-4.4	6-4.4
D15S128	4-*	4-4	1-3	4-1-3
GABRB3	3-*	6-3	8-8	6-8-8
D15S97	4-*	3-4	5-5	3-5-5

Fig. 5. Segregation of DNA polymorphic markers of chromosomes 21 and 15. Alleles 6 (Kb) and 4.4 (Kb) at the D15S63 locus, represent the methylated and unmethylated alleles, respectively. Asterisks: one allele is missing in fully informative markers. In the markers D21S11, GABRB3 and D15S97 that were not fully informative, the relative intensity of the bands indicated that they existed in double doses.

boy (II-2) had partial trisomy 15 (pter > q15) and partial monosomy 21 (pter > q22.1). The translocation breakpoint on chromosome 15 was not determined but according to the cytogenetic results it was distal to the PWS/AS critical region (q11.2-q13). The breakpoint on chromosome 21 was at 21q22.1 within 4 cM (2.3 Mb on the physical map) [McInnis et al., 1993; Lawrence et al., 1993] between the polymorphic markers D21S217 and D21S213. Thus, the unbalanced segment of chromosome 21 spans from pter to ~4 cM distal to the APP gene and it does not include the SOD1 gene [Lawrence et al., 1993]. Although several patients with a similar translocation were described [Chettouh et al., 1995], none of them had the same molecular breakpoints and in all of them the breakpoint was distal to the SOD1 gene.

In order to delineate the phenotypic effect of the imbalance in chromosome 21 in our patients, we had to exclude the contribution of the chromosome 15 imbalance to their phenotype. The most striking phenotype of patient IL-1 was that of PWS which is associated with del(15)(q11.2 > q13). It should be noted that patient II-1 had typical PWS, although her deletion in 15q was larger than in the typical 4 Mb deletion typically seen in PWS [Nicholls, 1993]. The comparison of the clinical manifestations of patient II-1 to those reported in partial trisomy 21 [Korenberg et al., 1994] and in PWS, is presented in Table II. Nine clinical traits scored by Korenberg et al. [1994] were present in patient II-1. None of those are specific to trisomy 21, mental retardation, hypotonia, up-slanted palpebral fissure and short stature are common to PWS and DS, while congenital dislocation of the hip and flat feet are probably secondary to hypotonia and short neck can be secondary to the obesity. The abnormal dermatoglyphics including the low main line index and the presence of large digital loops in the hallucal areas are typical of PWS [Reed and Butler, 1984; Smith and Simpson, 1982]; the high a-b ridge count was not reported in PWS. It seems that in this patient the Prader-Willi syndrome dominated the clinical presentation and masked the effect of the partial trisomy 21.

Patient II-2 had partial trisomy 15 (pter > q15) and partial monosomy 21 (pter > q22.1). Partial trisomy of proximal 15q is clinically variable [Clayton-Smith et al., 1993; Fryns, 1990]. Among the findings that are accounted for by partial trisomy 15q are mental retardation, intrauterine and postnatal growth retardation, microcephaly, large nose, cleft palate, malpositioned ears and limb anomalies [Fryns, 1990]. Mental retardation and malpositioned ears were present in patient II-2. Since the segment 15q1 includes imprinted genes,

TABLE II. Clinical Findings in Patients II-1 and II-2

Partial trisomy 21	Patient II-1	Patient II-2	Partial monosomy 21
Mental retardation[b]	Moderate[a]	Moderate	Mental retardation[c,d]
Short stature[b]	+[a]	–	Short stature[d]
Microcephaly	–	–	Microcephaly[d]
Brachycephaly	–	–	
Flat face	–	–	
	–	–	Prominent occiput
	+	+	Low hair line[c]
	–	–	Broad/"fish mouth"
Palpebral fissure[b]	Up-slanted[a]	Down-slanted	
Epicanthus	–	–	
	–	–	Hypertelorism
Brushfield spots	–	–	
Flat nasal bridge	–	–	
	–	–	Large nose[d]
Highly-arched palate	–	–	
Furrowed tongue	–	Deep central groove	
Open mouth	–	–	
	–	–	Highly arched palate[d]
	–	–	Retrognatia
Malpositioned ears	–	Protruding	Malpositioned ears[c,d]
Dysmorphic ears	–	Large	Large ears[c]
Short neck[b]	+	+	Short neck[c]
Cardiac anomaly	–	–	
Duodenal stenosis	–	–	
Broad short hand	–	–	
Brachydactyly	–	–	
Clinodactyly 5	–	–	
Wide gap, toes 1 and 2	–	+	
Dermatoglyphics	Abnormal[a]	Abnormal	
Palmar crease	–	–	
Hypotonia[b]	Hypotonia[a]	Hypertonia	Hypertonia[c]
Lax ligaments	Flat feet	–	
Cong. dislocation of hip	+	–	
	NA	+	Cryptorchidism[c]
	–	+	Kyphosis[c]
	–	+	Joint contractures[c]
	–	–	IUGR[d]
	Convulsion	–	
	Hypopigmentation[a]	–	
	Rapid weight gain[a]	–	
	Myopia[a]	–	
	–	–	syndactyly of toes[d]

[a] Clinical signs that can be attributed to PWS.
[b] Clinical signs that were described in patients with partial trisomy 21 [Korenberg et al., 1994].
[c] Clinical signs that were described in patients with partial monosomy 21 [Chettouh et al., 1995].
[d] Clinical signs that can be attributed to partial trisomy 15q1 [Fryns, 1990].

it is probable that the parental origin of the extra copy of 15q1 is an important factor in the determination of the phenotype in partial trisomy 15q1. In patient II-2, the duplication of 15q1 was paternally derived. Other patients with similar but not identical karyotype were described [Chettouh et al., 1995; Rethoré et al., 1973]. One of them was a de novo carrier of the translocation 46,XX,−21,t(15;21)(q1209;q22.102). NOR staining of the der(15) of the translocation indicated that it was of paternal origin. The two other patients were a brother and a sister with the karyotype 46,XX or XY,−21,+der (15)t(15;21)(q13;q22.1) of maternal origin. Patient II-2 is as similar to the patient with partial trisomy 15 of paternal origin as to the two sibs with partial trisomy 15 of maternal origin. Anomalies of patient II-2 that are common to cases with partial monosomy 21 pter > q22.1 [Courtens et al., 1994; Chettouh et al., 1995; Huret et al., 1995] are large ears, short neck, cryptorchidism, hypertonia, arthrogryposis-like symptoms and mental retardation. Except for malpositioned ears, mental retardation and IUGR none of them are common in partial trisomy 15q1.

In a recent study, Chettouh et al. [1995] correlated the phenotypes of 6 patients with partial monosomy 21 to the cytogenetic and molecular breakpoints on chromosome 21. They suggested that monosomy of the APP-SOD1 region contributes to the pathogenesis of 10 out of 25 clinical signs of monosomy 21. Patient II-2 had 6 of the 10 clinical traits scored by Chettouh et al. [1995], including short neck, low hairline, large ears, arthrogryposis-like symptoms, hypertonia and mental retardation (Table II). In addition he had kyphosis and cryptorchidism that were assigned to the region 21cen> D21S11 that is within the monosomic 21 segment of patient II-2. However, he did not have a large nose, ocular

hypertelorism, highly arched palate and transverse palmar crease that were assigned to the APP-SOD1 segment by Chettouh et al. [1995]. The monosomic 21 segment in patients II-2 did not include the SOD1 gene nor did it include the GIuR5 gene which was mapped distal to the D21S213 locus [Chettouh et al., 1995]. Thus, patient II-2 may refine the "critical region" from APP-SOD1 to APP-D21S213 and define a new region at D21S213-SOD1.

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